

FOIPA PTO-1390 (REV. 12-2001)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER	
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371				U.S. APPLICATION NO. (If none, see 37 CFR 1.5) 10/069343	
INTERNATIONAL APPLICATION NO. PCT/JP00/05642		INTERNATIONAL FILING DATE 23 August 2000 (23.08.00)		PRIORITY DATE CLAIMED 24 August 1999 (24.08.99)	
TITLE OF INVENTION Methods of Pasteurizing/Sterilizing Immune Substance Containing Antiinflammatory Factor and Utilization Thereof					
APPLICANT(S) FOR DO/EO/US ORTHO CORPORATION CO., LTD. and NOMOTO, Kikuo					
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:					
1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input type="checkbox"/> The US has been elected by the expiration of 19 months from the priority date (Article 31). 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) a. <input checked="" type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).					
Items 11 to 20 below concern document(s) or information included:					
11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. 14. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A change of power of attorney and/or address letter. 17. <input type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825. 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input type="checkbox"/> Other items or information:					

U.S. APPLICATION NO. (if any) 10/069343 INTERNATIONAL APPLICATION NO. PCT/JP00/05642		ATTORNEY'S DOCKET NUMBER 2443	
21. <input type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)): Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(I)-(4) \$710.00 International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(I)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT :		CALCULATIONS PTO USE ONLY	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(c)).		\$ 890.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	6 -20 -	0	x \$18.00
Independent claims	2 -3 -	0	x \$84.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$280.00
TOTAL OF ABOVE CALCULATIONS		-	\$ 890.00
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.		+	\$ 445.00
SUBTOTAL		-	\$ 445.00
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			\$
TOTAL NATIONAL FEE		=	\$
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property+			\$
TOTAL FEES ENCLOSED		-	\$ 445.00
		Amount to be refunded:	\$
		charged:	\$
a. <input type="checkbox"/> A check in the amount of \$ _____ to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>501241</u> A duplicate copy of this sheet is enclosed. d. <input checked="" type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.			
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.			
SEND ALL CORRESPONDENCE TO: <div style="display: flex; justify-content: space-between; align-items: flex-start;"> <div style="width: 60%;"> <p style="font-size: 1.2em; margin: 0;"><i>Customer No. 7617</i></p> <p>CHARLES E. BRUZGA The Law Office of Charles E. Bruzga 11 Broadway, Suite 400 New York, NY 10004</p> </div> <div style="width: 35%; text-align: right;"> <p style="font-size: 1.2em; margin: 0;"><i>Charles E. Bruzga</i></p> <p>SIGNATURE</p> <p>Charles E. Bruzga</p> <p>NAME</p> <p>28,935</p> <p>REGISTRATION NUMBER</p> </div> </div>			

Rec'd PCT/PTO 08 JUL 2002 1006 5343 100202 #

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Naoyuki Kamata

Serial No. 10/069,343

Patent No.:

Filed: Rec'd PCT/PTO 22-Feb-2002

For: Methods of Pasteurizing/Sterilizing
Immune Substance Containing
Antiinflammatory Factor and
Utilization Thereof

Attorney Docket No. 2443

Group Art Unit:

Examiner:

Allowed on:

Batch No.:

Assistant Commissioner for Patents
Washington, D.C. 20231

SECOND PRELIMINARY AMENDMENT & CHANGE OF CUSTOMER NUMBER

Please replace claims 1-6 with the following set of claims 1-12.

- 1. (Amended) A method for sterilizing an immune substance containing anti-inflammatory factors, comprising heating a solution of said immune substance containing antiinflammatory factors at a temperature of from 55 to 70° C for 30 to 60 minutes.
2. A method for sterilizing an immune substance containing anti-inflammatory factors, comprising filtering the solution of said immune substance containing antiinflammatory factors by a filter with pore size of from 0.1 to 0.22 microns.
3. (Once amended) A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 1.
4. (Once amended) Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method according to Claim 1.

5. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 2.
6. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method of Claim 2.
7. A method for sterilizing an immune substance containing anti-inflammatory factors, consisting essentially of heating a solution of said immune substance containing antiinflammatory factors at a temperature of from 55 to 70° C for 30 to 60 minutes.
8. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 7.
9. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method according to Claim 7.
10. A method for sterilizing an immune substance containing anti-inflammatory factors, consisting essentially of filtering the solution of said immune substance containing antiinflammatory factors by a filter with pore size of from 0.1 to 0.22 microns.
11. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 10.
12. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method of Claim 10.--

REMARKS

Claims

The present amendment adds two independent claims, so that the total number of independent claims is increased from 2 to 4. A credit card payment form authorizes payment of \$42.00 for presenting 1 independent claim more than 3.

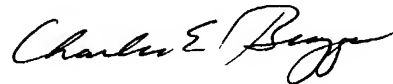
In particular, claims 1 and 3 have been amended to change "characterized by" to "comprising," which is more commonly used in U.S. practice. Claim 7 is similar to claim 1, but uses "consisting essentially of" rather than "comprising." Claim 10 is similar to claim 2, but replaces "comprising" with "consisting essentially of." Thus claims 7 and 10 would exclude processes involving exposure to temperature sufficient to drastically reduce the activity of the immunopotentiating factors, such as discussed with respect to Example 2 in the specification (pages 15-16). New claims 7-8 and 11-12 are similar to original claims 2 and 3, respectively.

Customer Number

Please change customer no. 7617 to 07617.

Dated: July 1, 2002

Respectfully submitted,



Charles E. Bruzga
Attorney for Applicant
Customer No. 07617

MARKED-UP FULL SET OF CLAIMS TO SHOW CHANGES MADE

--1. (Amended) A method for sterilizing an immune substance containing anti-inflammatory factors, ~~characterized by~~ comprising heating a solution of said immune substance containing antiinflammatory factors at a temperature of from 55 to 70° C for 30 to 60 minutes.

2. A method for sterilizing an immune substance containing anti-inflammatory factors, ~~characterized by~~ comprising filtering the solution of said immune substance containing antiinflammatory factors by a filter with pore size of from 0.1 to 0.22 microns.

3. (Once amended) A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 1.

4. (Once amended) Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method according to Claim 1.

5. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 2.

6. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method of Claim 2.

7. A method for sterilizing an immune substance containing anti-inflammatory factors, consisting essentially of heating a solution of said immune substance containing antiinflammatory factors at a temperature of from 55 to 70° C for 30 to 60 minutes.

8. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 7.

9. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method according to Claim 7.

10. A method for sterilizing an immune substance containing anti-inflammatory factors, consisting essentially of filtering the solution of said immune substance containing antiinflammatory factors by a filter with pore size of from 0.1 to 0.22 microns.

11. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 10.

12. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method of Claim 10.--

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JC19 Rec'd PCT/PTO 22 FEB 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Naoyuki Kamata

Serial No. Based on PCT/JP00/05642 *filed*

23-Aug-2000

Patent No.:

Filed:

For: Methods of Pasteurizing/Sterilizing
Immune Substance Containing
Antiinflammatory Factor and
Utilization Thereof

Attorney Docket No. 2443

Group Art Unit:

Examiner:

Allowed on:

Batch No.:

Assistant Commissioner for Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Please replace claims 1-4 with the following set of claims 1-6:

- 1. A method for sterilizing an immune substance containing anti-inflammatory factors, characterized by heating a solution of said immune substance containing antiinflammatory factors at a temperature of from 55 to 70° C for 30 to 60 minutes.
2. A method for sterilizing an immune substance containing anti-inflammatory factors, characterized by filtering the solution of said immune substance containing antiinflammatory factors by a filter with pore size of from 0.1 to 0.22 microns.
3. (Once amended) A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 1.
4. (Once amended) Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method according to Claim 1.

5. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 2.

6. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method of Claim 2.—

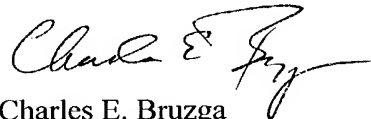
REMARKS

The present amendment eliminates multiple-dependent claims from the application. Accordingly, the application now contains six total claims, two of which are in dependent form.

I hereby certify that on February 22, 2002, this document, a PTO form 1390, a credit card payment form and the Japanese-language PCT application are being deposited with the US Postal Service as Express Mail Post Office to Addressee No. EV051313935US to Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231.

Dated: February 22, 2002

Respectfully submitted,



Charles E. Bruzga
Attorney for Applicant
Customer No. 7617

MARKED-UP FULL SET OF CLAIMS TO SHOW CHANGES MADE

1. A method for sterilizing an immune substance containing anti-inflammatory factors, characterized by heating a solution of said immune substance containing antiinflammatory factors at a temperature of from 55 to 70° C for 30 to 60 minutes.
2. A method for sterilizing an immune substance containing anti-inflammatory factors, characterized by filtering the solution of said immune substance containing antiinflammatory factors by a filter with pore size of from 0.1 to 0.22 microns.
3. (Once amended) A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to ~~either~~ Claim 1 ~~or~~ 2.
4. (Once amended) Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method according to ~~either~~ Claim 1 ~~or~~ 2.
5. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to Claim 2.
6. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing antiinflammatory factors sterilized and/or pasteurized by the method of Claim 2.

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SPECIFICATION

METHOD OF PASTEURIZING/STERILIZING IMMUNE SUBSTANCE CONTAINING
5 ANTIINFLAMMATORY FACTOR AND UTILIZATION THEREOF

TECHNICAL FIELD

10 The present invention relates to the pasteurization and/or sterilization of an immune
substance containing antiinflammatory factors, and in particular to a method for pasteurizing
and/or sterilizing an immune substance containing antiinflammatory factors, where the
substance is susceptible to heat, without damaging their effects, and to the use of the immune
substance containing antiinflammatory factors that have been pasteurized and sterilized by
15 these methods.

BACKGROUND ART

20 The term inflammation is "a localized protective response elicited by injury or
destruction of tissues, which serves to destroy, dilute or wall off both the injurious agent and
the injured tissue," and is accompanied by signs of "pain, fever, flare, edema, and loss of
function," etc. (Dorland's Medical Dictionary). The antiinflammatory agent is generally
used for the nosotropic to the inflammation. Known antiinflammatory agents include

antihistamines, both steroidal and non-steroidal antiinflammatory agents, antiinflammatory enzymes, and immunosuppressants.

5 A major problem caused by the antiinflammatory agents, however, is their side-effects or adverse reactions. In case of salicylates, for example, which are very commonly used as antiinflammatory medicine, especially well-known aspirin, but a heavy dosage may cause central respiratory paralysis and circulatory collapse, presenting a cause of epigastralgia, nausea, vomiting, or gastrointestinal bleeding.

10 In view of the above, it is highly desirable to develop antiinflammatory agents without causing any side-effects or adverse reaction. An antiinflammatory composition derived from cow milk has been proposed as a candidate antiinflammatory agent with no side-effect or adverse reaction (Japanese Laid-open Patent Applications (Tokukai) Sho57-188523 and Sho59-61316), and also the isolation and use of antiinflammatory factors
15 as an antiinflammatory medicine have been proposed. (Published Japanese Translation of PCT International Publication for Patent Application (Tokuhyo) Hei2-503802, Hei8-502515, Hei8-502718, and Hei10-509420).

20 The present invention is directed to providing a technology where an immune substance containing antiinflammatory factors derived from the aforementioned cow milk is used as so-called health food. As used hereinbelow, an immune substance containing antiinflammatory factors means an immune substance comprising a mixture of milk protein fraction and low molecular-weight fraction having a molecular-weight of 10,000 or less, wherein both fractions are isolated from whey which can be obtained upon the removal of fat

and casein from milk of female mammal, which mammal being hyperimmunized by the adjuvant-vaccine made from attenuated or killed germs, attenuated or inactivated viruses, or toxoids. The milk protein fraction and the low molecular-weight fraction with the molecular-weight of 10,000 or less can be isolated from whey by means of, for example, chromatographic separation, separation by gel filtration or ultrafiltration. The methods disclosed in Published Japanese Translation of PCT International Publication for Patent Application (Tokuhyo) Hei2-503802, Hei8-502515, Hei8-502718, and Hei10-509420) can be also applied thereto.

10 The immune substance containing antiinflammatory factors has some effect on improving the enteric conditions, immunopotential and antiinflammation effects on animals and human beings. The substances may be administered orally or through anus in the form of solution, powder, granules or addition to food products. Some specific effects include, for example, the amelioration of enteric conditions and constipations, the prophylaxis and care of carcinoma in colon, opportunistic infection, neoplastic transformation, relaxation of immunodeficiency disorders, prevention and care of periodontal disorders including gingivitis, ulcerative disorders, relaxation of rheumatic symptoms, as well as prevention and care of asthma.

20 The immune substance containing antiinflammatory factors is a useful substance beneficial for showing effects on the antiinflammation and immunization without any adverse effects. Those antiinflammatory effects can be verified, for example, by the air-pouch method. The principle of the air pouch method is as follows. The procedure of the method is to administer orally an antiinflammatory substance to mice, then forming a

hypodermic air-pouch (air cavity) under the skin of the mice and infusing carrageenan (an irritant), then finally counting the migrating white blood cells. Because the inflammation is associated with the leucocytes migrating and infiltrating to the infected area, the more leucocytes are counted, the more severe is the inflammation. On the contrary, the stronger the antiinflammatory action is, the fewer leucocytes are found to migrate and infiltrate.

On the other hand, the immune substance containing antiinflammatory factors are particularly susceptible to heat, that is, their effectiveness will be lost when exposed to elevated temperatures. On the other hand, heating methods are employed for pasteurization and/or sterilization of most foods. Thus, the characteristic of the immune substance containing antiinflammatory factors where its activeness is lost by heat is a major impediment when it is used as a health food. In this aspect, a method for pasteurization and/or sterilization that would not impede the effect of immune substance containing antiinflammatory factors would have a significant meaning when they are used as so-called health foods.

Therefore an object of the present invention is to overcome the above drawback of the immune substance containing antiinflammatory factors and thereby to provide methods for pasteurizing and/or sterilizing the substances without impeding their effectiveness. Another object of the present invention is to use as health foods the immune substance containing antiinflammatory factors thus pasteurized and/or sterilized.

DISCLOSURE OF THE INVENTION

The invention in accordance with Claim 1 discloses a method for pasteurizing and/or sterilizing immune substance containing antiinflammatory factors, characterized by heating a solution of the immune substance containing antiinflammatory factors to 55 to 70°C for 30 to 60 minutes. The invention in accordance with Claim 2 discloses a method for pasteurizing and/or sterilizing immune substance containing antiinflammatory factors, characterized by filtering the solution of the immune substance containing antiinflammatory factors by a filter with pore size of 0.1 to 0.22 microns. The invention in accordance with Claim 3 discloses substances including the immune substance containing antiinflammatory factors which has been pasteurized and/or sterilized by the method according to Claim 1 or 2. The invention in accordance with Claim 4 discloses ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, frozen fruit, mayonnaise, dressing, and other food products or drinks, to which there has been added the immune substance containing antiinflammatory factors pasteurized and/or sterilized by the method according to Claim 1 or 2.

Since the immune substance containing antiinflammatory factors are relatively new substances, many aspects as to their properties and usage have not been well explained. The conditions best suited for the pasteurization and sterilization of the immune substance containing antiinflammatory factors are not yet determined. The present invention has been made so as to be the first to elucidate those conditions of the pasteurization and sterilization of the immune substance containing antiinflammatory factors.

The method described in Japanese Laid-open Patent Application (Tokukai)

Hei4-66050, involves heating at 62°C for 30 minutes and at 75°C for 15 seconds, as an example of a method for pasteurizing the milk containing immunoglobulins. This method is related only to the milk containing immunoglobulins and not to the immune substance containing antiinflammatory factors of the present invention. As can be seen, the
5 pasteurization and/or sterilization of the immune substance containing antiinflammatory factors is basically different from the pasteurization of milk containing immunoglobulin.

Specifically, the immune substance containing antiinflammatory factors is a mixture of the milk protein fraction and the low molecular-weight fraction with a molecular-weight
10 of 10,000 or less, both of which may be isolated from whey obtained upon the removal of milk fat and casein. The substance does not contain milk fat, lactose, casein, and the like which are normally contained in the milk. The susceptibility to the heat of the immune substance containing antiinflammatory that contain neither milk fat, lactose, casein, or the like is remarkable in comparison with the one having those components. It is not necessary
15 to be pointed out that other methods of pasteurization and/or sterilization are required for the substances that do contain lactose, casein, and the like, different from those that do not.

The present invention may not provide the immune substance containing antiinflammatory factors for use in medicines, but rather, the present invention seeks to find
20 their application to foods and thereby utilizing the so-called health foods. One major feature of the present invention may allow the immune substance containing antiinflammatory factors to be pasteurized and/or sterilized for use in the health foods, without significantly damaging their effectiveness.

The inventors perfected the present invention upon discovering the most suitable conditions by heating to a specific temperature range or filtering by a filter with small pore size for the pasteurization and sterilization of the immune substance containing antiinflammatory factors without damaging their effects. The invention is directed to providing food products obtained by adding thereto the immune substance containing antiinflammatory factors pasteurized and/or sterilized by the inventive methods as explained above, said food products being useful as health foods showing antiinflammatory and immunopotential effects.

10

BEST MODE EMBODIMENTS FOR CARRYING OUT THE INVENTION

The present invention will be illustrated with reference to some embodiments thereof. The immune substance containing antiinflammatory factors is first dissolved in water to obtain an aqueous solution. The concentration of the substance in the aqueous solution is approximately from 0.01 to 20 % by weight. The aqueous solution is then subjected to a heat process at a temperature of 55 to 70°C for 30 to 60 minutes. This procedure allows the immune substance containing the antiinflammatory factor to be pasteurized and sterilized without impairing the antiinflammatory and immunopotential effects. Although the temperature and the period of time of the procedure have factors to be determined in a relation of each to the other, the temperature itself is important. The inventors have recognized that the process temperature beyond 70°C resulted in antiinflammatory effects significantly deteriorated. As the pasteurization and/or sterilization may not be satisfactorily achieved when the process temperature is too low, the

process needs to be carried out at a temperature of at least 55°C or over. The process should be conducted within the temperature range of from 55 to 70°C so as to effectively pasteurize and/or sterilize the immune substance containing antiinflammatory factors.

5 The aqueous solution of the immune substance containing antiinflammatory factors thus pasteurized and sterilized may be used as such, or in the form of either powder or concentrate after being freeze-dried or dried at a low temperature to be added ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, and other foods or drinks. The solution or powder of the immune substance containing
10 antiinflammatory factors may be added by a suitable amount to the raw material of each foregoing item, and thereby to finish the food production process in a commonly known manner for each food and drink item. Depending on the material used, the solid content of the immune substance containing the antiinflammatory factor is about 1 to 20 % by weight, but may not be limited thereto. The addition of an amount of the immune substance of the
15 order as described above may show favorable antiinflammatory and immunopotential effects. Because each of the aforementioned materials does not involve any process where it is subjected to high temperatures, in particular, the pasteurized and/or sterilized aqueous solution can be effectively used.

20 Alternatively, the aqueous solution of the immune substance containing antiinflammatory factors can be also pasteurized and sterilized by filtration using a filter with pore size of 0.1 to 0.22 microns. Since bacterial germs do not pass through a filter having pores in the size above, pasteurization and sterilization may be obtained by treating with the filter. The filter used in this instance may be made of a membrane and the like comprised of

cellulose mixed thereto. As for the filtration process, an aqueous solution of the immune substance containing antiinflammatory factors at a concentration of 20% or less may be filtered out under pressure at a temperature at which the substance may not be changed, for example, 40°C or below.

5

The aqueous solution of the immune substance containing antiinflammatory factors pasteurized and sterilized by the filtration may be used in ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, and dressing or other foods or drinks in the manner similar to the case of the aqueous solutions of the immune substance containing

10 antiinflammatory factors pasteurized and sterilized by heat, as described above.

In both methods of pasteurizing and sterilizing the immune substance containing antiinflammatory factors by heat or filter, the process is applied to aqueous solutions. Although the source material must be in the form of solution while processing, it may not

15 necessarily be an aqueous solution. Any solvent other than water, such as an aqueous solution of ethyl alcohols or ethyl alcohol may be used instead, to the extent that the activity of the immune substance containing antiinflammatory factors is not compromised.

The solution of the immune substance containing antiinflammatory factors

20 pasteurized and/or sterilized by heat or filter may be directly added as such to food and drink products, or may be added in a form of concentrate or powder after being freeze-dried or drying at a low temperature, as have been described previously.

Some exemplary uses of the immune substance containing antiinflammatory factors

thus pasteurized and/or sterilized will be illustrated in detail with reference to the following embodiments. The case of ice cream will be first described. The immune substance containing antiinflammatory factors sterilized by filtration may be added to starting materials such as milk, cream, eggs, and flavoring, by the amount of about 10 % by weight. The materials were thoroughly mixed in a homogenizer, and the resulting mixture was pasteurized by heating at 68°C for 30 minutes. The pasteurized mixture was cooled to 2 to 5°C and then overrun at -15°C to entrain air thereby to obtain an ice cream. The ice cream thus obtained is a health food having the antiinflammatory and immunopotentiating effects. The immune substance containing antiinflammatory factors which have been sterilized by filtering or heating process may also be added after the new material mixture of the ice cream is subjected to the pasteurization process.

Mayonnaise can be obtained by mixing and emulsifying pasteurized egg yolk, fragrances and flavoring, salad oil, and the immune substance containing antiinflammatory factors (15 % by weight) which has been sterilized by heating at 68°C for 30 minutes. This mayonnaise may be provided as a health food. There is no need to say that the immune substance containing antiinflammatory factors, which have been sterilized by filtration, may be equally used.

The immune substance containing antiinflammatory factors (12 % by weight) which has been pasteurized or sterilized by heating at 68°C for 30 minutes, or by filtering with a filter with pore size of 0.22 microns, emulsifier, flavoring, etc. were mixed to finely ground cocoa beans, then the mixture was tempered at 65°C and molded into a predetermined shape, to make a chocolate. Such chocolate may similarly be provided as a

health food.

A mixture of strawberries and the immune substance containing antiinflammatory factors (12 % by weight) which had been sterilized by filtering with a filter having pore size of 0.22 microns, was heated to 68°C. The mixture was concentrated at the same temperature in vacuo, then pectin was added followed by sterilization by heating at 68°C for 30 minutes. Alternatively, the immune substance containing antiinflammatory factors (12 % by weight) may be added to the strawberries at the same time as pectin is added. Strawberry jam containing the immune substance containing antiinflammatory factors (12 % by weight) was thus obtained. It is needless to say that a variety of fruits can be used in lieu of strawberries.

A liquid type drink potion was added to the immune substance containing antiinflammatory factors (18 % by weight), and then filtered by a filter having pore size of 0.22 microns, to obtain a potion containing the immune substance containing antiinflammatory factors. The drink potion may alternatively be subjected to a heat process at 68°C for 30 minutes after the immune substance containing antiinflammatory factors is added thereto.

A case where it is applied to yogurt will be described below. Yogurt may be classified into plain yogurt, hard yogurt, soft yogurt, yogurt drinks, frozen yogurt, and so forth. Since the plain yogurt is the basic one, the case of a plain yogurt is described herebelow.

The immune substance containing antiinflammatory factors was pasteurized by heating at 65°C for 30 minutes, then cooled to a temperature of from 45 to 48°C. Meanwhile, milk was prepared with additives added thereto as needed, and then heated, mixed, and homogenized, followed by the milk mixture being sterilized at a temperature of 90 to 95°C. The milk after the sterilization process was then cooled to a temperature of between 45 and 48°C, and the immune substance containing antiinflammatory factors also cooled to from 45 to 48°C was added to and mixed with the milk, and then the starter was added thereto and mixed. The mixture was put into a fermentation container thereby to promote the fermentation. It was cooled to the room temperature to obtain the product. When an aqueous solution of stabilizer and flavoring are added to the milk during the process, it may change into a hard yogurt. In case of hard yogurt, by grinding the curd after fermentation and cooling to a temperature of between 5 and 20°C, and then followed by a fruit sauce being added and mixed to obtain the product, a soft yogurt is obtained as the end product.

The effects of the methods of pasteurization and/or sterilization of the immune substance containing antiinflammatory factors in accordance with the present invention will be further described in the following examples.

Example 1

Mice were orally administered with an antiinflammatory substance, followed by a subcutaneous air pouch (air cavity) being formed, and then by carrageenan (irritant) being injected, and whereby the leucocytes migrating to the local region was counted. Four

samples selected for this examination were as follows:

(1) Commercially available milk: skim milk by Morinaga Milk Industries, Co. Ltd., was dissolved in purified water at a concentration of 60 % by weight.

5

(2) S-100 milk: powdered skim milk prepared from cow milk immunized (vaccinated) to 26 kinds of killed germs of pathogenic micro organisms was dissolved in purified water at a concentration of 60 % by weight.

10

(3) WPI+ solution: an 8:2 mixture of the protein fraction of whey isolated from S-100 milk and the low molecular-weight antiinflammatory fraction of whey, called MUF, similarly isolated by the ultrafiltration of S-100 milk, was dissolved in purified water at a concentration of 0.16 % by weight.

15

(4) MDF solution: antiinflammatory fraction isolated from S-100 milk by the ion exchanger column was dissolved in purified water at a concentration of 0.1 % by weight.

The protocol used were as follows:

20

(1) mice at 9-weeks (strain C3H) were used.

(2) starting at 3 weeks before the test day, each mouse was given orally a daily dosage of 0.5 milliliter of either one of: control solution (saline), commercially available milk solution (i.e., 300 mg dosage for each), S-100 milk solution (i.e., 300 mg dosage for each),

WPI+ solution (i.e., 5 to 30 mg dose for each), and MDF solution (i.e., 5 mg dosage for each) through the peroral route.

(3) 6 days before the test, 2.5 milliliters of filtered air was hypodermically injected
5 to the dorsal region to form an air pouch.

(4) 3 days before the test, 2.5 milliliters of filtered air was injected in the same subcutaneous pouch region as in (2) to secure the pouch.

10 (5) 1 hour before the test, the last dosage was administered orally.

(6) 1 mg of carrageenan (0.1 milliliter of 1 W/V% solution) was injected by a syringe into the air pouch.

15 (7) After 4 hours, using a syringe, the air pouch was irrigated by 2 milliliters of PBS (phosphate-buffered saline) for 3 times to wash out cells in the air pouch

(8) The saline suspensions containing collected cells were centrifuged by a centrifuge separator.

20

(9) After supernatant of samples was discarded until a total amount of 1 milliliter of the liquid with cells suspended therein was obtained, and the cell suspensions were thoroughly mixed.

(10) The samples containing the cells were stained with Turk's staining solution. Each sample was mixed with Turk's solution at a ratio of 1:9. After the hemolysis, the leucocytic nuclei were then shown stained.

5 (11) The number of WBC contained in each sample was counted using a Turk's leucocyte plate (hemocytometer) (mean of the counts of 4 sectors will be multiplied by 10^4). Table 1 gives the measurements each indicating the number of cells infiltrated into the air pouch.

10 In terms of the number of infiltrated leucocytes, the commercially available milk showed approximately same results as the control. S-100 milk, WPI+ solution, and MUF, on the other hand, showed counts of infiltrating white blood cells lower than the control, suggesting their antiinflammatory effect. The counts of WPI+ solution depended proportionally on the dosage, and resulted in fewer counts at higher doses, indicating that the
15 antiinflammatory effect depends on the dosage of WPI+. The WPI+ is a type of immune substance containing antiinflammatory factors according to the present invention.

Example 2

20 2 grams of the immune substance containing antiinflammatory factors were dissolved in water to make a total volume of 20 milliliters. The solution was further diluted with SMUF (buffer solution at pH 6.6) to make 0.02% solution. 1 milliliter portions of the solution were respectively dispensed to centrifuge tubes to incubate in the following conditions: at 75°C for 30 minutes, at 70°C for 30 minutes, at 65°C for 30 minutes, at 55°C

for 30 minutes, and no heating. After the process, each sample was centrifuged at 10,000 G for 10 minutes. 0.5 milliliter supernatant was separated from each tube. Respective samples supernatant of 250-microliter each were respectively mixed with the same amounts of SMUF to yield test specimens of 0.01%. The optical density of each test specimen was measured by a microplate reader, and the residual activity of the antiinflammatory factor was determined by comparing with a separately prepared calibration curve. The results are shown in Table 2. The residual activities are represented as relative values (%), where the activity level at the room temperature is scaled to 100 (%).

As can be seen from Table 2, it is prominent that the residual activity of the immunopotentiating factors falls rapidly beyond 70°C, indicating that the process temperature of 70°C is a critical point. The residual activity of the immunopotentiating factors was held at least 80% or higher for the process temperatures up to 68°C, while the activity is nearly halved at 70°C, and virtually disappeared at 75°C.

Example 3

The effect of pasteurization and sterilization was examined in this example. 2 grams of immune substance containing antiinflammatory factors were taken to be dissolved in water to make a total volume of 20 milliliters. One colony of *Escherichia coli* cultured in a separate medium was added thereto and suspended in the solution. Part of the test solution was taken, and heated at 55, 60, and 65°C each for 30 minutes. The remainder of the solution was cooled to freezing temperature. 0.1 milliliter of the heated test solution and 0.1 milliliter of test solution at freezing temperature were each diluted with sterilized PBS to

make 10 milliliters of inoculating samples.

Nutrient agar and MacConkey's agar were each mixed with purified water, heated, and autoclaved for sterilization. Both agars were dispensed to sterile plastic plates and left
 5 to coagulation thereby to prepare flat culture beds each. Instruments were sterilized then set up in a clean bench for inoculating under an aseptic environment. 100 microliters samples were each dispensed on respective agars prepared as described above, and were uniformly applied thereto with glass rods. The plates were placed in an incubator maintained at 37°C and they were incubated for 24 hours. After 24 hours of incubation, the numbers of
 10 developed colonies were counted. The results are shown in Table 3.

There were 93 colonies grown in the general nutrient agar medium in case of the unheated sample, whereas no growth found in case of the sample heated to 65°C or higher. There were 4 colonies in case of the sample heated to 60°C, and 3 in case of the samples
 15 heated to 55°C. These results indicate that heating to 55°C or above may achieve the pasteurization, and heating to 65°C or above may achieve the sterilization, i.e., no colony may be present.

The results of Examples 2 and 3 show that the temperature range where both the
 20 preservation of the activity of antiinflammatory and the pasteurization and/or sterilization can be obtained lies in the range of from 55 to 70°C. The temperature range from 55 to 70°C may be thus the best suited condition for pasteurization and sterilization without deactivating antiinflammatory factor.

Example 4

Example 4 shows the sterilization and/or pasteurization by a filter. The filter used was FM-22 (the diameter is 47 mm, and the pore size is 0.22 microns) available from Fuji Photo Film Co. Ltd., and the filter unit was that supplied from Shibata Kikai Kagaku Kogyo K.K. 2 grams of the immune substance containing antiinflammatory factors was taken to be dissolved in water to make a total volume of 20 milliliters. The solution was centrifuged at 10,000 G for 10 minutes, and the supernatant thereof was collected. The sample solution was subjected to a filtration process by the sterilized filtration unit having the filter installed therein. The filtrate was diluted with sterilized PBS (phosphate-buffered saline) to prepare test solutions of 0.8% and 1.2%.

RID (radial immunodiffusion) kit commercially available from The Binding Site Inc. was used to determine the activity of antiinflammatory factor, where the sheep albumin PBS solution included in the kit was used for the control. Samples were dispensed to wells to be incubated at the room temperature for 72 hours. The diameter of precipitation circles was measured using a caliper. The data was used to obtain the equation for the calibration curve, then the equation was used in the data processing to calculate the activity of antiinflammatory factors in the samples each. The results are shown in Table 4.

20

For the assayed activity of the antiinflammatory factors, Table 4 gives the detected concentrations, the activity levels, and the residual activities where raw sample was rated to 100%, and the mean of residual activities. Each sample showed almost the same value regardless of whether being subjected to a filtering process or not. It should be understood

that the values of the heated samples exceeded by about 1%, the variance is within the tolerance of reproducibility guaranteed by the kit itself and is not to be considered as a problem. It was found that the activity of the filtered antiinflammatory factors is not changed by the filtration process.

5

Example 5

A similar procedure to Example 3 above was used to determine the viable count. 2 grams of the immune substance containing antiinflammatory factors was taken to be dissolved in water to make a total volume of 20 milliliters. One colony of separately
10 cultured E. coli was added and suspended in the solution. 10 milliliters of this solution was subjected to a filtration process by using a sterilized filtration unit having a filter installed therein. 0.1 milliliter of the filtered sample solution and 0.1 milliliter of untreated sample solution were each diluted with sterile PBS respectively to prepare 10 milliliters of
15 specimens.

Instruments were sterilized and set up in a clean bench for inoculation under an aseptic environment. 100 microliters of each sample were dispensed to respective agar plates prepared separately, and were uniformly applied with glass rods. The plates were
20 placed in an incubator and incubated at 37°C for 24 hours. After 24 hours of incubation, the number of developed colonies was counted. The results of colony count are shown in Table 5.

There were 708 colonies in the unfiltered sample on the general nutrient agar, and

no growth of colony was observed in the filtered samples. There were 394 colonies in the unfiltered sample on the MacConkey's agar, and no growth of colony was observed in the filtered sample. Two types of medium, namely nutrient agar for nonselective culture and MacConkey's agar for Escherichia specific culture, were used for inoculation. Growth of E. coli was found on both agars with unfiltered samples inoculated, however no colony growth was found with filtered samples on either medium. It should thus be recognized that pasteurization and/or sterilization was achieved by the filtration process.

In view of the foregoing, it should be understood that the filtration of the solutions of the immune substance containing antiinflammatory factors makes it possible for the substance to be sterilized, pasteurized, and disinfected without impairing the properties of the immune substance containing antiinflammatory factors.

15 INDUSTRIAL APPLICABILITY

The solution of the immune substance containing antiinflammatory factors may be sterilized, disinfected, and/or pasteurized by heating the solution in the temperature range of from 55 to 70°C or by filtering with a filter having pore size of 0.1 to 0.22 microns without deteriorating their effects. The immune substance containing antiinflammatory factors which have been thus pasteurized and sterilized may be added to a wide range of foods and drinks, and thereby providing useful products as health foods.

Table 1

Number of cells infiltrated into the air pouch ($\times 10000$ count)

5

Sample	1	2	3	4	5	6	7	8	9	Average	Standard Deviation	Significant Difference
Control	287	355	303	280	338	361	375	313	351	329.2	29.75	—
Commercially available milk	262	350	333	310	296	329	301	312	203	299.6	30.59	None
S-100 milk 300mg	48	55	62	81	68	88	60	76	59	66.3	10.59	P<0.005
WPI+ solution 300mg	32	31	26	27	21	30	41	48	31	31.9	5.63	P<0.005
WPI+ solution 20mg	133	109	100	90	128	113	89	121	154	115.2	16.69	P<0.005
WPI+ solution 10mg	226	248	291	299	268	271	265	254	278	266.7	16.37	P<0.005
WPI+ solution 5mg	312	256	263	321	291	301	284	300	268	288.4	18.40	P<0.05
MDF solution 5mg	16	21	43	18	22	15	30	32	25	24.7	6.96	P<0.005

5

Effect of process temperature on residual activity immunopotentiating factors

Process Temperature (°C)	Optical Density	Activity Level (ng/ml)	Average (ng/ml)	Rate of Residual Activities (%)
7 5	0. 076	0. 22	0. 11	0. 3
	0. 064	0		
7 0	0. 269	49. 7	49. 95	59. 3
	0. 271	50. 21		
6 8	0. 350	70. 46	69. 82	82. 9
	0. 345	69. 18		
6 5	0. 366	74. 56	74. 69	88. 7
	0. 367	74. 82		
5 5	0. 403	84. 02	81. 86	97. 3
	0. 386	79. 69		
Room Temperature	0. 399	83. 02	84. 17	100. 0
	0. 408	85. 33		

Table 3

5 Effect of process temperature on E. coli colonies

Sample	Number of Colonies
Unheated	9 3
Heated to 65°C	0
Heated to 60°C	4
Heated to 55°C	3

Table 4

Effect of filtering process on residual activities of antiinflammatory factors

Sample		Detected Concentrations (mg/l)	Activity Levels (mg/g)	Residual Activities (Average) (%)	
Raw Sample	0.8%	288.3	36.0	100.0	100.0
	1.2%	410.7	34.2	100.0	
Heated Sample	0.8%	293.0	36.6	101.6	101.5
	1.2%	416.2	34.7	101.3	

5

Table 5

Effect of filtration process on number of E. coli colonies

10

Sample	Nutrient Agar	MacConkey's Agar
Unfiltered	7 0 8	3 9 4
Filtered	0	0

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What is claimed is:

1. A method for sterilizing an immune substance containing anti-inflammatory factors, characterized by heating a solution of said immune substance containing antiinflammatory factors at a temperature of from 55 to 70° C for 30 to 60 minutes.
- 5 2. A method for sterilizing an immune substance containing anti-inflammatory factors, characterized by filtering the solution of said immune substance containing antiinflammatory factors by a filter with pore size of from 0.1 to 0.22 microns.
- 10 3. A substance containing said immune substance containing antiinflammatory factors, sterilized and/or pasteurized by the method according to either Claim 1 or 2.
4. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise, dressing, or other foods or drinks with added thereto the immune substance containing
15 antiinflammatory factors sterilized and/or pasteurized by the method according to either Claim 1 or 2.

ABSTRACT

The present invention provides methods for pasteurizing and/or sterilizing an
5 immune substance containing antiinflammatory factors without damaging their
antiinflammation and immunopotential effects, and the utilization of thus pasteurized
and/or sterilized substances as health foods.

Specifically, methods for pasteurizing and/or sterilizing an immune substance
10 containing antiinflammatory factors are provided by heating the solution of the immune
substance containing antiinflammatory factors at a temperature of from 55 to 70°C for 30
to 60 minutes, or by filtering the solution through a filter having pore size of from 0.1 to 0.22
microns. Ice cream, yogurt, liquid drinks, jam, butter, cheese, cream, sherbet, mayonnaise,
dressing, and other foods or drinks with the immune substance containing antiinflammatory
15 factors, which are pasteurized and sterilized by the present methods, added thereto are also
provided.

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(54) Title: METHODS OF PASTEURIZING IMMUNE SUBSTANCE CONTAINING ANTIINFLAMMATORY FACTOR AND UTILIZATION THEREOF

(54) 発明の名称: 抗炎症因子含有免疫性物質の殺菌方法及びその利用

(57) Abstract: Methods of pasteurizing/sterilizing immune substances containing antiinflammatory factors without damaging the antiinflammatory and immunopotentiating effects of the substances and utilization of the thus pasteurized/sterilized substances as health foods. Namely, methods of pasteurizing/sterilizing immune substances containing antiinflammatory factors which comprises heating a solution of the immune substances at a temperature of 55 to 70°C for 30 to 60 minutes, or filtering through a filter of 0.1 to 0.22 μ m in pore size. Foods and drinks such as ice cream, yogurt, liquid drink, jam, butter, cheese, cream, sherbet, mayonnaise, dressing and the like containing the immune substances containing antiinflammatory factors which have been pasteurized/sterilized by the above methods.

(57) 要約:

本発明は、抗炎症因子含有免疫性物質の抗炎症効果、免疫強化効果を損なうことなく、該物質の殺菌、滅菌を行う方法及びこのようにして殺菌、滅菌した該物質の健康食品としての利用を提供するものである。

即ち、抗炎症因子含有免疫性物質の溶液を55～70℃の温度で30～60分間熱処理する、ポアサイズ0.1～0.22 μ mのフィルターで濾過する抗炎症因子含有免疫性物質の殺菌、滅菌方法である。また、これらの方法で殺菌、滅菌した抗炎症因子含有免疫性物質を添加した、アイスクリーム、ヨーグルト、液体ドリンク、ジャム、バター、チーズ、クリーム、氷菓、マヨネーズ、ドレッシング、その他の食品、飲料類である。

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Methods of Pasteurizing/Sterilizing Immune
- Substance Containing Antiinflammatory Factor
and Utilization Thereof

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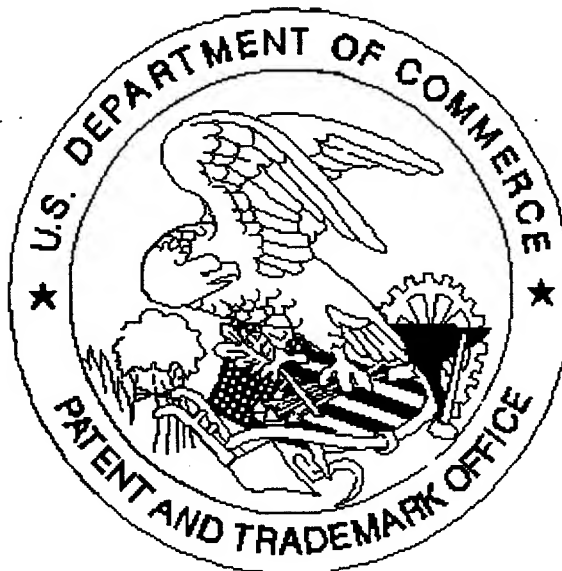
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